Remarks

Reconsideration of this Application is respectfully requested.

Claims 1-4, 6, 7 and 24-30 are pending in the application, with claim 1 being the sole independent claim. According to the Office Action dated December 13, 2005, claims 24, 26 and 28-30 are withdrawn from consideration.

Based on the following remarks, Applicant respectfully requests that the Examiner reconsider all outstanding rejections and that they be withdrawn.

I. Withdrawal of Claims 24, 26 and 28-30 From Consideration

According to the Office Action, claims 24, 26 and 28-30 are directed to inventions that are "independent or distinct from the invention originally claimed." (Office Action dated December 13, 2005, pages 2-3). Applicant respectfully disagrees and requests that claims 24, 26 and 28-30 be considered by the Examiner and examined on the merits.

Claim 24 depends from claim 1 and specifies that the human gene products (which are upregulated or expressed only during infection) result from mycobacterial infection. According to the Examiner, "[t]he new invention represents an unrelated invention to those previously claimed in that different functions are being performed in screening for vaccine targets for viral infections than is performed in screening for vaccine targets for mycobacterial infections." (Office Action dated December 13, 2005, pages 2-3). Applicant notes that independent claim 1, as presented prior to Applicant's last amendment, recited:

> . . . (a) identifying human gene products selected from the group consisting of: human gene products which are upregulated by a factor of 9 or greater during *infection* and human gene products which are expressed only during *infection* . . .

The previously presented claims did not specify the nature of the infection and therefore encompassed *any* infection. As noted in the specification:

> The method of the present invention can be used to screen for antigens which are differentially expressed in cells infected with *any infectious agent*, including viruses, fungal agents, *mycobacteria*, bacteria or parasitic agents.

(Specification, page 8, lines 5-7, emphasis added). Thus, contrary to the Examiner's assertion, the subject matter of claim 24 is *not* "unrelated" to the invention previously claimed, but is simply a species of the subject matter encompassed by the previously presented claims. The Examiner even acknowledged this fact at page 3 of the Office Action ("It is noted that claim 1, as previously presented would have been generic to the different types of infections . . .")

Moreover, a full and complete examination of the subject matter of the previously presented claims should have encompassed an examination of the methods wherein the human gene products result from mycobacterial infection, especially since the specification explicitly recites "mycobacteria" as one of the exemplary infectious agents. Clearly, claim 24 does not represent an independent or distinct invention from the invention previously claimed.

A similar analysis applies to claims 26 and 28-30. These claims depend from claim 1 and specify that the immune response (which is screened for in step (b) of claim

1) is an antibody response (claim 26), a T helper response (claim 28), inflammation (claim 29), or cytokine production (claim 30).

Independent claim 1, as presented in Applicant's Preliminary Amendment, filed on May 17, 2004, recited: ". . . (b) screening said host cell gene products for immunogenicity . . . " This claim did not specify any manner by which immunogenicity was to be screened and therefore encompassed *any* method for screening immunogenicity. According to the specification:

> "Immune response" encompasses humoral and cell-mediated immune responses, including, but not limited to, antibody response, cytotoxic T lymphocyte response, T helper response, inflammation, cytokine production, and complement.

(Specification, page 11, lines 16-20). Methods of the invention which comprise screening human gene products for an antibody response, a T helper response, inflammation, and cytokine production cannot properly be regarded as independent or distinct inventions from the previously presented methods. A proper examination of the previously presented claims should have included an examination of methods which comprise screening the human gene products for an antibody response, a T helper response, inflammation, and cytokine production, especially since these exemplary immune responses are explicitly set forth in the specification.

In view of the foregoing discussion, Applicant submits that the methods encompassed by claims 24, 26 and 28-30 are not independent or distinct from the methods encompassed by the previously presented claims. Applicant therefore respectfully requests that claims 24, 26 and 28-30 be fully considered by the Examiner and examined on the merits.

II. Claim Rejections Under 35 U.S.C. § 112, First Paragraph -- Enablement

Claims 1-4, 6, 7, 25 and 27 were rejected under 35 U.S.C. § 112, first paragraph, for lack of enablement. According to the Examiner, these claims contain "subject matter which was not described in the specification in such a way as to enable one skilled in the art to use the claimed method to identify potential vaccines for any infectious disease." (Office Action, page 4). Applicant respectfully traverses this rejection for the reasons set forth in Applicant's previous responses. Applicant provides the following additional remarks.

A. A Prima Facie Case of Lack of Enablement Has Not Been Established

The Examiner is respectfully reminded that, in order to make a rejection for lack of enablement, the Examiner has the initial burden to establish a reasonable basis to question the enablement provided for the claimed invention. *See* M.P.E.P. § 2164.04, citing *In re Wright*, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993). To satisfy this burden, the Examiner must provide "acceptable evidence or reasoning" to support an assertion of lack of enablement. *See In re Marzocchi*, 439 F.2d 220, 224, 169 USPQ 367, 370 (CCPA 1971). Here, the Examiner has not provided evidence or sound scientific reasoning to suggest that the practice of the currently claimed methods would not have enabled a person of ordinary skill in the art to identify potential vaccine targets for infectious diseases. Indeed, the evidence of record weighs heavily in favor of adequate enablement for the claimed methods. Without presenting any specific evidence to back up the assertion of lack of enablement, the rejection cannot properly be maintained.

A review of the present record reveals a striking attempt on the part of the Examiner to shift the burden to Applicant to prove that the invention *is enabled*, rather than presenting specific evidence or reasoning to show that the invention is *not enabled* as required under the law. For example, in the Office Action dated February 25, 2003, the Examiner explained the basis for the enablement rejection as follows: "These claim[s] are rejected because the applicant has not shown that the claimed method would be effective in identifying potential therapeutics for any infectious disease." (Office Action, dated February 25, 2003, page 4). This sentiment was reiterated in subsequent Office Actions. For example, in the Office Action dated December 16, 2004, the Examiner stated that "the rejection is not on the basis that the claimed method would not be able to identify host cell gene products that may induce a CTL response. Rather, the rejection is on the grounds that the Applicant has not demonstrated that such products would be useful as vaccines against any infectious disease." (Office Action dated December 16, 2004, page 3). It is clear from these passages that the Examiner is requiring Applicant to prove enablement of the invention before the Examiner has provided any evidence to suggest non-enablement.

The improper burden shifting in the context of this rejection is especially evident from the language used in the Office Action dated July 15, 2003:

> The rejection was on the basis that the Applicant has not shown that the claimed method of identifying potential vaccines would in fact identify potential vaccines. As was discussed in pages 6-7 of the prior action, the art surrounding the Applicant's invention gives no indication that the host cell genes that are differentially expressed (up-regulated) during viral infection would be effective vaccine targets against infectious diseases.

(Office Action dated July 15, 2003). The so-called "art surrounding the Applicant's invention," cited at pages 6-7 of the February 25, 2003 Office Action, in no way suggests that the claimed methods would *not* identify potential vaccine targets, and in fact, the Examiner did not even alleged that the cited art would not identify potential vaccine targets; rather, the Examiner simply asserted that the cited art "gives no indication that the host cell genes that are differentially expressed (up-regulated) during viral infection would be effective vaccine targets against infectious diseases." In other words, according to the Examiner, the cited art does not provide a definitive demonstration that the methods *are* enabled. An enablement rejection cannot be maintained on the ground that the prior art fails to demonstrate that the invention *would work* when there is no evidence of record to suggest that the invention *would not work*.

In the present Office Action, the Examiner stated that:

> As was indicated in the prior actions, the art indicates that there is a significant amount of uncertainty in the use of such up-regulated proteins as targets for anti-infection vaccines. In particular, the teachings of the Herberts and the Hickman references indicate that while self antigens may be helpful in the clearance of infections, it is not clear if this would be the case, or if the use of such antigens would lead to immunopathogenic autoimmunity. Herberts, Human Immunol 64: 44-55, at 53; and Hickman, J Immunol 171:22-26, at 26.

(Office Action dated December 13, 2005, page 5). Neither the Herberts nor the Hickman references suggest that gene products that are upregulated during infection would be ineffective as potential vaccine targets for infectious diseases. In fact, the Examiner has not even argued that Herberts and Hickman provide evidence that the claimed methods would not be enabled. Instead, the Examiner has simply made two assertions based on these references, neither of which satisfies the Examiner's burden of establishing a

reasonable basis to question the enablement provided for the presently claimed invention.

First, the Examiner asserted that the Herberts and Hickman references indicate that "self antigens may be helpful in the clearance of infections" but that "it is not clear if this would be the case." This assertion is unsupported by the references and is irrelevant to a proper enablement inquiry.

The relevant question in assessing the enablement of the present claims is whether there is any *evidence* to indicate or suggest that human gene products which are (1) upregulated by a factor of 9 or greater during viral or mycobacterial infection or are expressed only during viral or mycobacterial infection, and (2) that are identified as inducing an immune response in humans (selected from one of the recited immune responses), would not function as *potential* vaccine targets for infectious diseases. Neither Herberts nor Hickman nor any of the evidence of record provides any such indication or suggestion. Simply arguing that something "is not clear" from the cited references falls far short of establishing the requisite evidence to question the enablement of the presently claimed invention.

Second, the Examiner asserted that it is not clear from Herberts and Hickman "if the use of [self] antigens would lead to immunopathogenic autoimmunity." Again, asserting that something "is not clear" from a reference is not sufficient to establish a *prima facie* case of non-enablement.

Moreover, the question of whether self-antigens identified by the practice of the claimed methods may or may not induce autoimmunity is far outside the scope of a

proper enablement inquiry. At best, Hickman provides a hypothesis that virus-induced host epitopes could theoretically induce an autoimmune response. Even if Hickman's hypothesis is correct, this would have no bearing on the presently claimed invention: The present claims do not require that the identified *potential* vaccine targets not cause autoimmune reactions. Even if autoimmune reactions did occur, they would merely be a *side effect* of the potential vaccine targets. But whether or not the vaccine targets cause side effects is an issue for the FDA, not the PTO, and it has no relevance to the question of whether a person of ordinary skill in the art could have practiced the currently claimed methods without undue experimentation. *See, e.g., In re Anthony*, 414 F.2d 1383, 1395, 162 U.S.P.Q. 594, 604 (CCPA 1969) ("Congress has given the responsibility to the FDA, not to the [PTO], to determine . . . whether drugs are sufficiently safe . . . .") (citation omitted).

B. The Evidence of Record Overwhelmingly Supports Enablement

The fact that no specific evidence or clear scientific reasoning has been presented to cast doubt on the enablement provided for the presently claimed invention is reason enough to require withdrawal of the enablement rejection. Applicant nonetheless submits that the evidence of record strongly supports the enablement of the claimed methods. Of particular note in this regard is the Declaration of Dr. Donald F. Hunt, submitted with the Preliminary Amendment filed on May 17, 2004. According to Dr. Hunt:

> It is my opinion that, based on the specification and general knowledge of the art, a person of ordinary skill in the art would be able to use the methods of the present invention to identify potential vaccine targets. The plausibility of potential vaccine targets which are based on differentially

> expressed self-peptides is confirmed by Hickman *et al.*, which shows that overexpressed self-peptides may be presented in an MHC context; and Herberts *et al.*, and Veronese *et al.*, which both show an actual immune response against self-peptides overexpressed during infection.

(Hunt Declaration, ¶ 13). The Examiner has not provided any evidence or scientific reasoning to question the accuracy or validity of this *expert* opinion.

Dr. Hunt in his Declaration also pointed out that the use of self-peptides, which are differentially expressed in tumors, as tumor vaccines is well established in the art. In Dr. Hunt's words:

> Identification and use of vaccine targets which are self-peptides is prevalent in the field of tumor immunology. Several methods of vaccination using self-antigens are well known and studied, including vaccination with the peptides themselves, vaccination with polynucleotide vectors encoding the peptides, and treatment with autologous cells which have been exposed to the peptide.
>
> Vaccination with self-peptides has been shown effective in treating and preventing cancer. For example, Overwijk *et al.*, *Proc. Natl. Acad. Sci USA 96*:2982-2987 (1999) describes the immunization of mice with viral vectors encoding five different self-antigens which are overexpressed during melanoma. Overwijk *et al.* showed that vaccination with one of these viral vectors resulted in tumor protection in all mice studied.
>
> Given that tumor vaccines based on overexpressed self-peptides have been shown to be effective, and immune responses have been shown against self-peptides in infectious diseases, it is my opinion that one of ordinary skill in the art would expect to find potential vaccine targets for infectious diseases using the methods of the present invention. One of ordinary skill would also know how to actually make and test vaccines based on targets found through the claimed method.

(Hunt Declaration, ¶¶ 14-16). Again, the Examiner has not presented any evidence to challenge this opinion. In fact, it appears from the present Office Action that the Examiner admits that the use of self-antigens in tumor immunology is well established. According to the Examiner, "neither the teachings of Veronese or of the Hunt declaration

overcome the teachings of uncertainty in the art regarding the use of self-antigens to treat infectious diseases (*as opposed to cancers*)." (Office Action, page 5, emphasis added). The Examiner, however, has not pointed to any "teachings of uncertainty in the art regarding the use of self-antigens to treat infectious diseases." Rather, the rejection seems be based on a theory of autoimmune response induction which, as explained above, is irrelevant to the enablement inquiry.

Importantly, the Examiner has not explained why gene products that are upregulated in tumors *would* be effective as tumor vaccines, but gene products that are upregulated in infected cells *would not* be effective as potential vaccine targets -- The underlying scientific principles are exactly the same. The Examiner has provided no basis for discounting the expert Declaration of Dr. Hunt.

C. Summary

The Examiner has not presented any specific evidence or sound scientific reasoning to suggest that human gene products identified by the practice of the currently claimed methods would not be potential vaccine targets. Thus, the Examiner has not met his initial burden of establishing a *prima facie* case of lack of enablement. For this reason alone, the rejection should be withdrawn. In addition, the evidence of record -- including a Declaration by an expert in the art -- overwhelmingly suggests that human gene products identified by the practice of the currently claimed methods *would* be potential vaccine targets. Thus, Applicant respectfully requests that the rejection be reconsidered and withdrawn.

III. Claim Rejections Under 35 U.S.C. § 102

Claims 1-3 and 27 were rejected under 35 U.S.C. § 102(b) as being anticipated by Könen-Waisman *et al., J. Infectious Disease 179*:403-413 (1999) ("Könen-Waisman"). (Office Action, page 6). Applicants respectfully traverse this rejection.

An anticipation rejection under 35 USC § 102 requires a showing that each limitation of a claim is found in a single reference, practice, or device. *See In re Donohue*, 766 F.2d 531, 226 USPQ 619, 621 (Fed. Cir. 1985). Könen-Waisman fails to teach *any* of the elements of the presently claimed methods and therefore cannot anticipate the claims.

> First, the method of independent claim 1 comprises:
>
> (a) identifying human gene products selected from the group consisting of: human gene products which are upregulated by a factor of 9 or greater during viral or mycobacterial infection and human gene products which are expressed only during viral or mycobacterial infection.

Könen-Waisman does not teach the identification of a human gene product that is upregulated by a factor of 9 or greater during viral or mycobacterial infection, or a human gene product that is expressed only during viral or mycobacterial infection.

The bulk of Könen-Waisman relates to a peptide derived from a *mouse* hsp60 molecule called "p458m." This material therefore necessarily falls outside the scope of the present claims which involve the identification and screening of *human* gene products.

With regard to a human gene product, Könen-Waisman simply mentions that:

> Healthy persons are populated with T cells responsive to heat-shock protein (hsp) 60 epitopes of self as well as foreign origin, apparently from birth. Moreover, T cells reactive to hsp60 accumulate at sites of inflammation in large numbers, probably because the stress of inflammation and the activation of immune cells up-regulate expression of self hsp60 components on the surfaces of antigen-presenting cells.

(Könen-Waisman, page 403, right column). There is nothing in Könen-Waisman to indicate that human hsp60 was identified as being upregulated by a factor of 9 or greater during viral or mycobacterial infection, or that hsp60 was identified as a human gene product that is expressed only during viral or mycobacterial infection, as required by the present claims. For this reason alone, Könen-Waisman fails to teach every element of the currently claimed methods.

> The method of independent claim 1 also comprises:
>
> (b) screening said human gene products for an immune response in humans . . . wherein said immune response is selected from the group consisting of: antibody response, cytotoxic T lymphocyte (CTL) response, T helper response, inflammation, and cytokine production.

Nowhere in Könen-Waisman is it taught that human (or even mouse) hsp60 was screened for any of the recited immune responses *in humans*, as required by the present claims. Thus, this element of the present claims is also not taught by Könen-Waisman.

Since Könen-Waisman fails to teach all of the elements of any of the currently presented claims (indeed, Könen-Waisman fails to teach *any* of the elements of the currently presented claims), it follows that Könen-Waisman cannot and does not anticipate the currently presented claims. Applicants respectfully request that this rejection be reconsidered and withdrawn.

Conclusion

All of the stated grounds of rejection have been properly traversed, accommodated, or rendered moot. Applicant therefore respectfully requests that the Examiner reconsider all presently outstanding rejections and that they be withdrawn. Applicant believes that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Respectfully submitted,

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